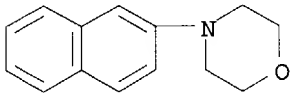
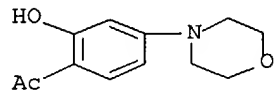
L8 ANSWER 450 OF 450 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1925:4542 CAPLUS
DN 19:4542
OREF 19:634e-f
TI Syntheses with β,β'-dichloroethyl ether
AU Cretcher, L. H.; Pittenger, W. H.
SO Journal of the American Chemical Society (1925), 47, 163-6
CODEN: JACSAT; ISSN: 0002-7863
DT Journal
LA Unavailable
OS CASREACT 19:4542
AB (ClCH2CH2)2O reacts with Na alkoxides to give substituted diethyl ethers: β-chloro-β' -methoxy, b744, 169°, d1516 1.0562, 58% yield; bis-[β-methoxy], b736 161.5°, d1515 0.9514, 36% yield; bis-[β-ethoxy], b735 187°, d1515 0.9149, 41% yield; bis-[β-propoxy], b737 219°, d1516 0.8877, 40% yield; bis-[β-butoxy], b741 250-2°, d1516 0.8847, 45% yield. Primary aromatic amines and (ClCH2CH2)2O, boiled with 35% aqueous NaOH, give morpholines: 4-p-tolyl, b30 167, m. 51°; 4-β-naphthyl, b30 239°, m. 90°; 4-α-naphthyl, m. 83°. The yields were about 35%. Na salts of organic acids react if a small amount of Et2NH is used as a catalyst. The following substituted diethyl ethers were prepared: bis-[β-acetoxy], b26 148°, d1515 1.1078, 45% yield; β-chloro-β'-benzoxy, b25 191°, d1615 1.1841, 44% yield; his-[β-benzoxy], b24 279-81, d1516 1.1701, 55% yield.
IT **7508-21-6**, Morpholine, 4-[2-naphthyl]-
(preparation of)
RN 7508-21-6 CAPLUS
CN Morpholine, 4-(2-naphthalenyl)- (9CI) (CA INDEX NAME)

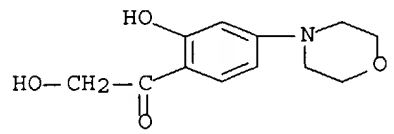


Related compound cl. 41

L4 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2004:7906 CAPLUS Full-text
TI DNA-dependent protein kinase inhibitors as drug candidates for the treatment of cancer
AU Kashishian, Adam; Douangpanya, Heather; Clark, Darcey; Schlachter, Stephen T.; Eary, C. Todd; Schiro, Justin G.; Huang, Hongmei; Burgess, Larry E.; Kesicki, Edward A.; Halbrook, James
CS ICOS Corporation, Bothell, WA, USA
SO Molecular Cancer Therapeutics (2003), 2(12), 1257-1264
CODEN: MCTOCF; ISSN: 1535-7163
PB American Association for Cancer Research
DT Journal
LA English
AB Cancer presents a difficult challenge for oncologists, as there are few therapies that specifically target disease cells. Existing treatment strategies rely heavily on phys. and chemical agents that nonspecifically affect DNA metabolism To improve the effectiveness of these treatments, we have identified a new class of protein kinase inhibitor that targets a major DNA repair pathway. A representative of this class, 1-(2-hydroxy-4-morpholin-4-yl-phenyl)-ethanone, inhibits the DNA-dependent protein kinase (DNA-PK) and differs significantly from previously studied DNA-PK inhibitors both structurally and functionally. DNA-PK participates in the cellular response to and repair of chromosomal DNA double-strand breaks (DSBs). These new selective inhibitors recapitulate the phenotype of DNA-PK defective cell lines including those from SCID mice. These compds. directly inhibit the repair of DNA DSBs and consequently enhance the cytotoxicity of phys. and chemical agents that induce DSBs but not other DNA lesions. In contrast to previously studied DNA-PK inhibitors, these compds. appear benign, exhibiting no toxic effects in the absence of DSB-inducing treatments. Most importantly, 1-(2-hydroxy-4-morpholin-4-yl- phenyl)-ethanone synergistically enhances radiation-induced tumor control in a mouse-human xenograft assay. These studies validate DNA-PK as a cancer drug target and suggest a new approach for enhancing the effects of existing cancer therapies.
IT **404009-40-1 404011-13-8**
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(DNA-dependent protein kinase inhibitors as drug candidates for treatment of cancer in relation to RPA phosphorylation)
RN 404009-40-1 CAPLUS
CN Ethanone, 1-[2-hydroxy-4-(4-morpholinyl)phenyl]- (9CI) (CA INDEX NAME)

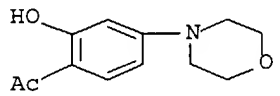


RN 404011-13-8 CAPLUS
CN Ethanone, 2-hydroxy-1-[2-hydroxy-4-(4-morpholinyl)phenyl]- (9CI) (CA INDEX NAME)



RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2003:830035 CAPLUS Full-text
DN 140:317212
TI Interactive Competition Between Homologous Recombination and Non-Homologous End Joining
AU Allen, Chris; Halbrook, James; Nickoloff, Jac A.
CS Department of Molecular Genetics and Microbiology, University of New Mexico School of Medicine, Albuquerque, NM, 87131, USA
SO Molecular Cancer Research (2003), 1(12), 913-920
CODEN: MCROC5; ISSN: 1541-7786
PB American Association for Cancer Research
DT Journal
LA English
AB DNA-dependent protein kinase (DNA-PK), composed of Ku70, Ku80, and the catalytic subunit (DNA-PKcs), is involved in double-strand break (DSB) repair by non-homologous end joining (NHEJ). DNA-PKcs defects confer ionizing radiation sensitivity and increase homologous recombination (HR). Increased HR is consistent with passive shunting of DSBs from NHEJ to HR. We therefore predicted that inhibiting the DNA-PKcs kinase would increase HR. A novel DNA-PKcs inhibitor (1-(2-hydroxy-4-morpholin-4-yl-phenyl)- ethanone; designated IC86621) increased ionizing radiation sensitivity but surprisingly decreased spontaneous and DSB-induced HR. Wortmannin also inhibits DNA-PKcs and reduces DSB-induced HR. IC86621 did not affect HR product outcome, indicating that it affects HR initiation. Thus, HR is increased in the absence of DNA-PKcs, but decreased when DNA-PKcs is catalytically inactive, suggesting interactive competition between HR and NHEJ. The effects of IC86621 and wortmannin were proportional to the level of DNA-PKcs, consistent with inhibited DNA-PKcs acting in a dominant neg. manner. We propose that inhibition of DNA-PKcs blocks its autophosphorylation, prevents dissociation of DNA-PKcs from DNA ends, and thereby blocks both HR and NHEJ. By blocking the two major DSB repair pathways, DNA-PKcs inhibitors should radiosensitize at all cell-cycle stages and are therefore excellent candidates for augmenting cancer radiotherapy.
IT **404009-40-1**, IC 86621
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(interactive competition between homologous recombination and non-homologous end joining: DNA-PKcs inhibitors as radiosensitizers)
RN 404009-40-1 CAPLUS
CN Ethanone, 1-[2-hydroxy-4-(4-morpholinyl)phenyl]- (9CI) (CA INDEX NAME)



RE.CNT 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2002:185097 CAPLUS Full-text
DN 136:247591
TI Preparation of arylmorpholines as inhibitors of DNA-dependent protein kinase and methods to potentiate cancer treatment
IN Halbrook, James; Kesicki, Edward; Burgess, Laurence E.; Schlachter, Stephen T.; Eary, Charles T.; Schiro, Justin G.; Huang, Hongmei; Evans, Michael; Han, Yongxin
PA Icos Corporation, USA
SO PCT Int. Appl., 247 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002020500	A2	20020314	WO 2001-US26709	20010828
	WO 2002020500	A3	20030731		
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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	US 2002165218	A1	20021107	US 2001-941897	20010828
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OS MARPAT 136:247591
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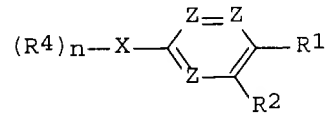

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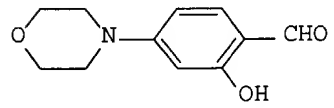


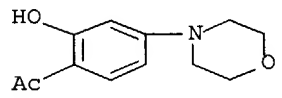
II

AB Compds. that inhibit DNA-dependent protein kinase, I [n = 0-4; X = (un)substituted 4-7 membered aliphatic ring containing 0-3 heteroatoms consisting of N, O and S (X = morpholinyl preferred); Z = independently N or CR3; R3 = independently H, halo, CHO, alkoxy, etc.; R1 = H, (un)substituted alkyl, cycloalkyl, CO, NO2, etc.; R2 = H, (un)substituted alkyl, carbamoyl, alkoxy, sulfamyl, etc.; with provision when X = morpholinyl, R2 and R4 and R3 = H at each occurrence, then R1 is different from COMe, phenylalkene, and NO2; and with the provision that when X = morpholinyl, R4 = H and Z = N at each occurrence, then R1 and R2 when taken together is different from triazole], were prepared

and compns. of I with other antineoplastic agents are claimed for use in cancer treatment therapy. Thus, II was prepared in 23% yield via formylation of 3-(4-morpholinyl)phenol. II demonstrated an IC50 value of 400 nM in DNA-PK assay. Preliminary results of animal tumor model studies indicate II enhanced the tumoristatic effect of total body irradiation (using 100-500 rad γ-radiation, II delayed tumor growth 1.2 to 1.8-fold relative to animals receiving radiation only).

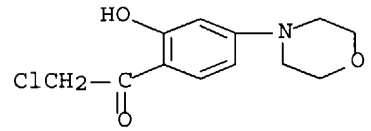
IT **404009-40-1P**
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(target compound; preparation of arylmorpholines as inhibitors of DNA-dependent protein kinase for cancer treatment)

RN 404009-40-1 CAPLUS
CN Ethanone, 1-[2-hydroxy-4-(4-morpholinyl)phenyl]- (9CI) (CA INDEX NAME)

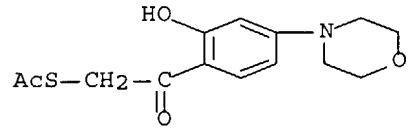


IT **404010-44-2P 404010-52-2P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(target compound; preparation of arylmorpholines as inhibitors of DNA-dependent protein kinase for cancer treatment)

RN 404010-44-2 CAPLUS
CN Ethanone, 2-chloro-1-[2-hydroxy-4-(4-morpholinyl)phenyl]- (9CI) (CA INDEX NAME)

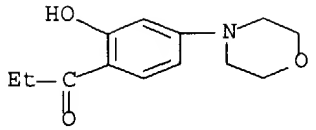


RN 404010-52-2 CAPLUS
CN Ethanethioic acid, S-[2-[2-hydroxy-4-(4-morpholinyl)phenyl]-2-oxoethyl] ester (9CI) (CA INDEX NAME)

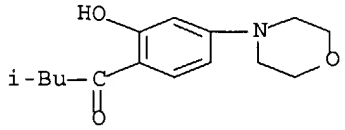


IT **404009-42-3P 404009-44-5P 404009-48-9P**
404010-36-2P 404010-38-4P 404010-45-3P
404010-46-4P 404010-47-5P 404010-51-1P
404010-53-3P 404011-13-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)(target compound; preparation of arylmorpholines as inhibitors of DNA-dependent protein kinase for cancer treatment)

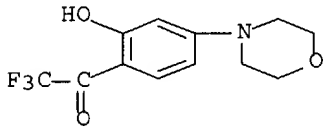
RN 404009-42-3 CAPLUS
CN 1-Propanone, 1-[2-hydroxy-4-(4-morpholinyl)phenyl]- (9CI) (CA INDEX NAME)



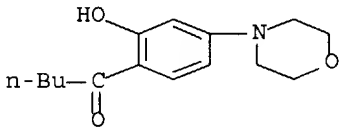
RN 404009-44-5 CAPLUS
CN 1-Butanone, 1-[2-hydroxy-4-(4-morpholinyl)phenyl]-3-methyl- (9CI) (CA INDEX NAME)



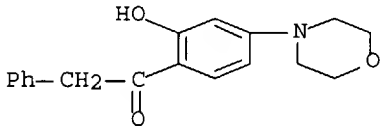
RN 404009-48-9 CAPLUS
CN Ethanone, 2,2,2-trifluoro-1-[2-hydroxy-4-(4-morpholinyl)phenyl]- (9CI) (CA INDEX NAME)



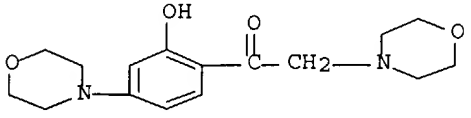
RN 404010-36-2 CAPLUS
CN 1-Pentanone, 1-[2-hydroxy-4-(4-morpholinyl)phenyl]- (9CI) (CA INDEX NAME)



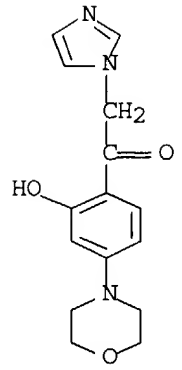
RN 404010-38-4 CAPLUS
CN Ethanone, 1-[2-hydroxy-4-(4-morpholinyl)phenyl]-2-phenyl- (9CI) (CA INDEX NAME)



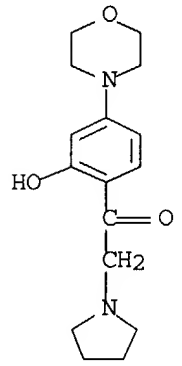
RN 404010-45-3 CAPLUS
CN Ethanone, 1-[2-hydroxy-4-(4-morpholinyl)phenyl]-2-(4-morpholinyl)- (9CI) (CA INDEX NAME)



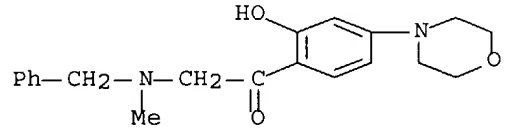
RN 404010-46-4 CAPLUS
CN Ethanone, 1-[2-hydroxy-4-(4-morpholinyl)phenyl]-2-(1H-imidazol-1-yl)- (9CI) (CA INDEX NAME)



RN 404010-47-5 CAPLUS
CN Ethanone, 1-[2-hydroxy-4-(4-morpholinyl)phenyl]-2-(1-pyrrolidinyl)-(9CI) (CA INDEX NAME)



RN 404010-51-1 CAPLUS
CN Ethanone, 1-[2-hydroxy-4-(4-morpholinyl)phenyl]-2-[methyl(phenylmethyl)amino]- (9CI) (CA INDEX NAME)



RN 404010-53-3 CAPLUS
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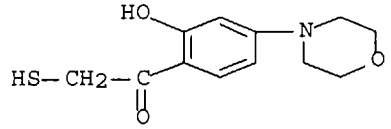
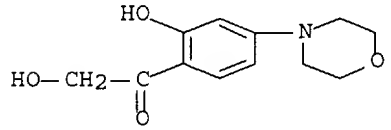


RN 404011-13-8 CAPLUS
CN Ethanone, 2-hydroxy-1-[2-hydroxy-4-(4-morpholinyl)phenyl]- (9CI) (CA INDEX NAME)



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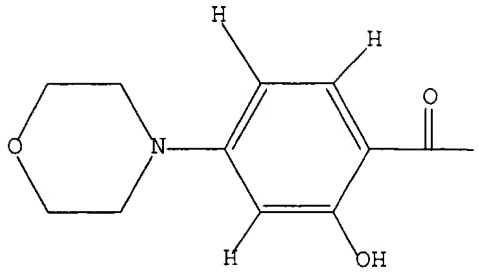
L1 STR



G1 C,O,S,N,P
G2 H,O,S,N,X

Structure attributes must be viewed using STN Express query preparation.

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FILE 'REGISTRY' ENTERED AT 16:41:57 ON 20 MAY 2004
L1 STRUCTURE UPLOADED
L2 0 S L1
L3 14 S L1 FUL

FILE 'CAPLUS' ENTERED AT 16:42:21 ON 20 MAY 2004
L4 3 S L3

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	15.15	170.78

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-2.08	-2.08

STN INTERNATIONAL LOGOFF AT 16:43:20 ON 20 MAY 2004